Group I

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: _____ Examiner # : _____ Date: _____
Art Unit: _____ Phone Number 30_____ Serial Number: _____
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Streptococcal Toxin C & Methods of Use

Inventors (please provide full names): Patrick M. Schlievert Duncan Chesney

David T. Mitchell Pamela Orihel

Earliest Priority Filing Date: 12/6/96

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search the claims 1-16 and the Inventors. Thanks

Point of Contact:
Beverly Shears
Technical Info. Specialist
CM1 12C14 Tel: 308-4994

Streptococcal toxin C
mutant
fragments
B-barrel, B-subunit
N-terminal region

Immunogenic Composition

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Beverly Shears 4994	NA Sequence (#) _____	STN _____
Searcher Phone #: _____	AA Sequence (#) _____	
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: 03/30/02	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: 12	Patent Family _____	WWW/Internet _____
Online Time: 23	Other _____	Other (specify) _____

PTO-1590 (1-2000)

Hines
09/336036

-key terms

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FILE 'CAPLUS' ENTERED AT 11:27:45 ON 30 MAR 2000
L1          46 SEA FILE=CAPLUS ABB=ON  PLU=ON  (SPEC OR SPE C)(S)STREPTO
               COCC?
L2         683 SEA FILE=CAPLUS ABB=ON  PLU=ON  STREPTOCOCC?(2A)C
L5          44 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L1 OR L2)(S)TOXIN
L6           1 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5(S)(MUTAT? OR MUTANT
               OR MUTAGEN? OR POLYMORPH? OR POLY MORPH?)

L1          46 SEA FILE=CAPLUS ABB=ON  PLU=ON  (SPEC OR SPE C)(S)STREPTO
               COCC?
L2         683 SEA FILE=CAPLUS ABB=ON  PLU=ON  STREPTOCOCC?(2A)C
L5          44 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L1 OR L2)(S)TOXIN
L7           3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 AND (MUTAT? OR MUTANT
               OR MUTAGEN? OR POLYMORPH? OR POLY MORPH?)

L8           3 L6 OR L7

=> d 1-3 .beverly

L8   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:        1998:398420  CAPLUS
DOCUMENT NUMBER:         129:53355
TITLE:                   Mutants of streptococcal
                         toxin C and use as vaccines
INVENTOR(S):             Schlievert, Patrick M.; Ohlendorf, Douglas;
                         Mitchell, David T.; Gahr, Pamala J.
PATENT ASSIGNEE(S):      Regents of the University of Minnesota, USA;
                         Schlievert, Patrick M.; Ohlendorf, Douglas;
                         Mitchell, David T.; Gahr, Pamala J.
SOURCE:                  PCT Int. Appl., 55 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE          APPLICATION NO.  DATE
     ----------          ----  --------      ---------------  --------
     WO 9824910          A2    19980611      WO 1997-US22125  19971205
         W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
            DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG,
            KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
            MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
            TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD,
            RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
            FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
            CM, GA, GN, ML, MR, NE, SN, TD, TG
     AU 9876256          A1    19980629      AU 1998-76256    19971205
                               Searcher  :    Shears  308-4994
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EP 946730 A2 19991006 EP 1997-949733 19971205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1996-33251 19961206
WO 1997-US22125 19971205

AB This invention is directed to **mutants** of Streptococcus pyrogenes exotoxin type C (SPE-C) or fragments thereof, vaccine and pharmaceutical compns., and methods of using the vaccine and pharmaceutical compns. The preferred SPE-C toxin has at least one amino acid change and is substantially non-lethal compared with the wild type SPE-C toxin. The **mutant** SPE-C toxins can form vaccine compns. useful to protect animals against the biol. activities of wild type SPE-C toxin. Single and double substitution **mutants** of SPE-C were prepd. with E. coli. Rabbits immunized with these recombinant toxins were protected from challenge by S. pyogenes.

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:305066 CAPLUS
DOCUMENT NUMBER: 129:91623
TITLE: Characterization of the hemolytic activity of Streptococcus equi
AUTHOR(S): Flanagan, J.; Collin, N.; Timoney, J.; Mitchell, T.; Mumford, J. A.; Chanter, N.
CORPORATE SOURCE: Animal Health Trust, Newmarket, Suffolk, CB8 7UU, UK
SOURCE: Microb. Pathog. (1998), 24(4), 211-221
CODEN: MIPAEV; ISSN: 0882-4010
PUBLISHER: Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The hemolytic activity of S. equi, the cause of equine strangles, was characterized. Prodn. of hemolysin in Todd Hewitt broth was dependent on an equine serum supplement and the logarithmic phase of growth after which activity declined sharply. RNA core also induced hemolysin prodn. from cells harvested at the end of the logarithmic phase of growth. Hemolysis was not affected by cholesterol, was only slightly increased in reducing conditions, and was completely inactivated by trypan blue, identifying the hemolytic activity as streptolysin S-like (SLS-like). Purifn. by hydroxyapatite and Sephacryl column chromatog. yielded proteins of mol. wts. of .apprx.6000 and 17,000-22,000 Da with a 64-fold increase in specific activity. Low-mol.-wt. proteins from the RNA core were still present in the purified toxin. Two non-hemolytic **mutants** were derived by conjugation with an Enterococcus faecalis-carrying transposon Tn916. Southern blots of HindIII digests of DNA revealed that one of the **mutants** contained three transposon insertions and the other just one. A lambda phage library of S. equi contained plaques whose hemolytic activity was enhanced by

reducing conditions and inhibited by cholesterol, suggesting a streptolysin O-like (SLO-like) activity. However, hemolysin in culture sonicates of host E. coli in which the lambda phage insert was subcloned into plasmid (pUC18) was not affected by those conditions. Seven isolates of S. equi in medium without SLS-like inducers showed no SLO-like activity and no evidence for an SLO-like **toxin** could be found by immunoblotting with pneumolysin antiserum and monoclonal antibodies or by polymerase chain reaction with primers derived from sequences conserved between the SLO genes of Lancefield group A, C, and G **streptococci**.
S. equi does not appear to possess a streptolysin O but does make a streptolysin S-like toxin whose prodn. can be interrupted at just one genetic locus.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:10032 CAPLUS
DOCUMENT NUMBER: 122:73341
TITLE: Molecular evolution of the staphylococcal and streptococcal pyrogenic toxin gene family
AUTHOR(S): Van Den Bussche, Ronald A.; Lyon, Julie D.; Bohach, Gregory A.
CORPORATE SOURCE: Dep. Biol. Sci., Univ. Idaho, Moscow, 83843, Russia
SOURCE: Mol. Phylogenet. Evol. (1993), 2(4), 281-92
CODEN: MPEVEK; ISSN: 1055-7903
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pyrogenic toxin (PT) family is composed of the staphylococcal enterotoxins (SE), the toxic shock syndrome toxin, and the streptococcal pyrogenic exotoxins (SPE). Whereas considerable effort has focused on characterization of PTs due to their unique biol. properties, the understanding of the evolution of this gene family is incomplete. Phylogenetic relationships for members of the PT family were estd. by examg. the previously reported nucleotide sequences of the genes encoding SPEA, SPEC, SEA, SEB, SEC1, SEC2, SEC3, SED, and SEE. Addnl., the authors present and analyze sequence data on seven previously unreported sec genes. Within the PT family, sequence divergence was partitioned in a hierarchical fashion such that mean sequence divergence ranged from 1.179 among all 16 toxin genes, 0.443 among those restricted to Staphylococcus, and 0.028 among the genes encoding 10 variants of Type C SE. Results of this study are interpreted as suggesting that the PT family consists of two large clades. One clade consists of the staphylococcal **toxins** SEA, SEE, and SED, being closely related to the **streptococcal toxin SPEC**, whereas the other clade depicts close relationships of the staphylococcal **toxins** SEC and SEB with the **streptococcal toxin** SPEA.

Searcher : Shears 308-4994

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, TOXLIT, TOXLINE' ENTERED AT 11:31:32 ON 30 MAR 2000)
L9 21 S L8
L10 11 DUP REM L9 (10 DUPLICATES REMOVED)

L10 ANSWER 1 OF 11 TOXLINE
ACCESSION NUMBER: 1999:51995 TOXLINE
DOCUMENT NUMBER: CRISP-99-HL37260-12
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH MED & RES CTR, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R37HL37260-12
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904
AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome **toxin** (TSST-KS) or **streptococcal** pyrogenic exotoxin **C** (**SPEC**) that activates macrophages and induces the selective stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a risk factor for KS. We will assay anti-**toxin** antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of **toxin** neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of **toxin**-producing bacteria with various established parameters of immune activation in acute KS. The demonstration that isolation of **toxin** secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the

development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L10 ANSWER 2 OF 11 TOXLINE
ACCESSION NUMBER: 1999:51994 TOXLINE
DOCUMENT NUMBER: CRISP-99-HL36611-11
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: SCHLIEVERT P M
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R01HL36611-11
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904
AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic **toxin** superantigens, notably **streptococcal** pyrogenic exotoxins (SPEs, scarlet fever **toxins**), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome **toxin**-1, with the intent to clarify the molecular mechanism(s) of action of the **toxins** and develop toxoid

vaccines against the **toxins**. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient **toxins** for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic **toxin** superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L10 ANSWER 3 OF 11 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-333329 [29] WPIDS
DOC. NO. CPI: C1998-103377
TITLE: **Mutant** non-lethal Streptococcus pyrogenic exotoxin type C - useful for vaccines to protect from biological activity of wild type toxin e.g. to prevent or ameliorate streptococcal toxic shock syndrome.
DERWENT CLASS: B04 D16
INVENTOR(S): GAHR, P J; MITCHELL, D T; OHLENDORF, D; SCHLIEVERT, P M
PATENT ASSIGNEE(S): (MINU) UNIV MINNESOTA
COUNTRY COUNT: 79
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9824910	A2	19980611	(199829)*	EN	55

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV

MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
TR TT UA UG US VN YU ZW
AU 9876256 A 19980629 (199845)
EP 946730 A2 19991006 (199946) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9824910	A2	WO 1997-US22125	19971205
AU 9876256	A	AU 1998-76256	19971205
EP 946730	A2	EP 1997-949733	19971205
		WO 1997-US22125	19971205

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9876256	A	Based on	WO 9824910
EP 946730	A2	Based on	WO 9824910

PRIORITY APPLN. INFO: US 1996-33251 19961206
AN 1998-333329 [29] WPIDS
AB WO 9824910 A UPAB: 19980722
Mutant Streptococcus pyrogenic exotoxin type C (**SPE-C**) **toxin** (or fragment) having at least one amino acid change and substantially non-lethal compared to wild-type **SPE-C toxin** is new. Also claimed are: (1) vaccines containing **mutant toxin** for protecting animals against at least one biological activity of wild-type **SPE-C**; (2) DNA (I) encoding **mutant toxin**; (3) stably transformed host cells comprising (I).

USE - The **mutant toxins** are useful in vaccines which can be administered to animals (especially humans) to protect against at least one biological activity of a wild-type **SPE-C** (claimed). Such vaccines are especially useful to reduce symptoms associated with toxic shock (claimed) such as in human **streptococcal** toxic shock syndrome (STSS). **Streptococcus** pyogenes is a pathogen of humans which can cause mild infections e.g. impetigo or severe acute diseases e.g. scarlet fever and STSS. **SPE-C** is thought to be associated with STSS and has several proposed biological activities, e.g. has been shown to block liver clearance of endotoxin and act as a 'superantigen' i.e. induce T lymphocytes proliferation, resulting in abnormally high levels of circulating cytokines TNF- beta and IFN- gamma . Vaccines can also be produced using DNA encoding **mutant SPE-C toxin** (either

directly or in viral vectors) or stably transformed cells. The **toxin** can be included with a physiologically acceptable carrier in pharmaceutical compositions (claimed), useful therapeutically to stimulate T-cell proliferation. The **mutant toxins** are also useful to generate neutralising antibodies immunoreactive with both **mutant** and wild type **toxin**, useful as a passive immune serum to treat STSS.
Dwg.0/10

L10 ANSWER 4 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998202593 MEDLINE
DOCUMENT NUMBER: 98202593
TITLE: Characterization of the haemolytic activity of Streptococcus equi.
AUTHOR: Flanagan J; Collin N; Timoney J; Mitchell T; Mumford J A; Chanter N
CORPORATE SOURCE: Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk, CB8 7UU, U.K.
SOURCE: MICROBIAL PATHOGENESIS, (1998 Apr) 24 (4) 211-21. Journal code: MIC. ISSN: 0882-4010.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807

AB The haemolytic activity of Streptococcus equi, the cause of equine strangles, was characterized. Production of haemolysin in Todd Hewitt broth was dependent on an equine serum supplement and the logarithmic phase of growth after which activity declined sharply. RNA core also induced haemolysin production from cells harvested at the end of the logarithmic phase of growth. Haemolysis was not affected by cholesterol, was only slightly increased in reducing conditions and was completely inactivated by trypan blue, identifying the haemolytic activity as streptolysin S-like (SLS-like). Purification by hydroxyapatite and Sephacryl column chromatography yielded proteins of molecular weights of approximately 6000 and 17 000-22 000 Da with a 64-fold increase in specific activity. Low molecular weight proteins from the RNA core were still present in the purified **toxin**. Two non-haemolytic **mutants** were derived by conjugation with an Enterococcus faecalis-carrying transposon Tn916. Southern blots of HindIII digests of DNA revealed that one of the **mutants** contained three transposon insertions and the other just one. A lambda phage library of S. equi contained plaques whose haemolytic activity was enhanced by reducing conditions and inhibited by cholesterol, suggesting a streptolysin O-like (SLO-like) activity. However, haemolysin in culture sonicates of host E. coli in which the lambda phage insert was subcloned into plasmid (pUC18), was not

affected by these conditions. Seven isolates of S. equi in medium without SLS-like inducers showed no SLO-like activity and no evidence for an SLO-like **toxin** could be found by immunoblotting with pneumolysin antiserum and monoclonal antibodies or by polymerase chain reaction with primers derived from sequences conserved between the SLO genes of Lancefield group A, **C** and G **streptococci**. S. equi does not appear to possess a streptolysin O but does make a streptolysin S-like **toxin** whose production can be interrupted at just one genetic locus.

L10 ANSWER 5 OF 11 TOXLINE
ACCESSION NUMBER: 1998:60284 TOXLINE
DOCUMENT NUMBER: CRISP-98-HL37260-11
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH CENTER, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R37HL37260-11
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805

AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome **toxin** (TSST-KS) or **streptococcal** pyrogenic exotoxin **C** (**SPEC**) that activates macrophages and induces the selective stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a risk factor for KS. We will assay anti-**toxin** antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of **toxin** neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of **toxin**-producing bacteria with various

established parameters of immune activation in acute KS. The demonstration that isolation of **toxin** secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L10 ANSWER 6 OF 11 TOXLINE
ACCESSION NUMBER: 1998:60283 TOXLINE
DOCUMENT NUMBER: CRISP-98-HL36611-10
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: SCHLIEVERT P M
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 2R01HL36611-10
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805
AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic **toxin** superantigens, notably **streptococcal** pyrogenic exotoxins (SPEs, scarlet fever

toxins), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome **toxin**-1, with the intent to clarify the molecular mechanism(s) of action of the **toxins** and develop toxoid vaccines against the **toxins**. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient **toxins** for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic **toxin** superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L10 ANSWER 7 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 96183627 MEDLINE
DOCUMENT NUMBER: 96183627
TITLE: Genetic and phenotypic diversity among isolates of Streptococcus pyogenes from invasive infections.
AUTHOR: Chaussee M S; Liu J; Stevens D L; Ferretti J J
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, USA.
CONTRACT NUMBER: AI-19304 (NIAID)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1996 Apr) 173 (4) 901-8.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

Searcher : Shears 308-4994

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
AB To determine if recent cases of invasive group A **streptococcal** disease were caused by strains with a unique characteristic, 117 isolates **Streptococcus** pyogenes from patients with a variety of diseases, including necrotizing fasciitis and toxic shock syndrome, were analyzed. Significant genomic heterogeneity was observed among selected isolates, as determined using pulsed-field gel electrophoresis. The frequency of the bacteriophage-associated **streptococcal** erythrogenic **toxin** genes A and C (speA and **speC**) among the isolates was 44% (49/112) and 34% (38/112), respectively. Forty-three percent of speA-positive isolates produced **streptococcal** erythrogenic **toxin** (SPE) A in vitro. Seventy-six percent (85/112) of isolates produced SPE B in vitro, and in contrast to SPE A, little variation in the concentration of SPE B in broth culture supernatants was detected. The genetic and phenotypic heterogeneity observed among isolates from recent cases of severe infection does not support a clonal basis for the resurgence of invasive **streptococcal** infections.

L10 ANSWER 8 OF 11 TOXLINE
ACCESSION NUMBER: 1996:3920 TOXLINE
DOCUMENT NUMBER: CRISP-96-HL37260-09
TITLE: PATHOGENESIS AND ETIOLOGY OF KAWASAKI SYNDROME.
AUTHOR: LEUNG D Y
CORPORATE SOURCE: NATIONAL JEWISH CENTER, 1400 JACKSON STREET, DENVER, CO 80206
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 2R37HL37260-09
SOURCE: (1995). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199604
AB RPROJ/CRISP Kawasaki syndrome (KS) is currently the most common cause of acquired heart disease in children. Early treatment of KS with intravenous gammaglobulin significantly reduces, but does not eradicate, the occurrence of cardiovascular complications. Thus, discovery of the etiology and pathogenesis of KS is of critical importance. The current proposal will expand upon preliminary data from our lab that suggests the marked immune activation associated with acute KS is caused by a superantigen(s), e.g., a variant staphylococcal toxic shock syndrome **toxin** (TSST-KS) or **streptococcal** pyrogenic exotoxin **C** (**SPEC**

) that activates macrophages and induces the selective stimulation of T cells bearing Vbeta2 gene segments. The specific aims will be: First, to assess the role of antibody repertoire as a risk factor for KS. We will assay anti-**toxin** antibody levels in sera from acute vs convalescent KS patients, their family members and age-matched controls by using both functional assays of **toxin** neutralization and ELISA. We postulate that the selective deficiency of antibodies against TSST-KS and/or **SPEC** predispose to acute KS> Second, to correlate the isolation of **toxin**-producing bacteria with various established parameters of immune activation in acute KS. The demonstration that isolation of **toxin** secreting S. aureus is accompanied by the activation of macrophages and Vbeta2+ T cells will strengthen the argument that superantigens play a role in the pathogenesis of KS. Third, to determine whether the selective stimulation of T cells in patients with KS, complicated by the development of coronary artery disease, is oligoclonal or diverse, we will clone and sequence their T Cell Receptor Vbeta2 and control Vbeta gene transcripts amplified PCR. Fourth, to determine whether TSST-KS has different immunologic properties than staphylococcal TSST1 when tested on T cells, B cells, and/or vascular endothelial cells. We postulate that as the result of several critical **mutations** between variant TSST-KS vs staphylococcal TSST1, the cause of Toxic Shock Syndrome (TSS), that TSST-KS may exhibit different immunologic properties which account for at least some of the differences in the immunologic features distinguishing acute KS vs TSS. The importance of our proposed studies is that it should contribute directly to an understanding of the pathogenesis and etiology of KS. The elucidation of immune mechanisms underlying this disease will have important implications for the development of more effective therapeutic approaches to the treatment of KS as well as other diseases where similar pathologic mechanisms may exist. Furthermore, identification of the causative agent and unique populations of T cells associated with KS may allow us to more readily diagnose this disease and institute early therapy to prevent heart disease.

L10 ANSWER 9 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 93018037 MEDLINE
DOCUMENT NUMBER: 93018037
TITLE: Genetic diversity in T1M1 group A streptococci in relation to clinical outcome of infection.
AUTHOR: Norgren M; Norrby A; Holm S E
CORPORATE SOURCE: Department of Clinical Bacteriology, University of Umea, Sweden..
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1992 Nov) 166 (5) 1014-20.
Journal code: IH3. ISSN: 0022-1899.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199301
AB Genetic diversity was found at high frequency downstream of the emm1 gene among T1M1 group A **streptococci** (GAS) isolated in Scandinavia during a recent epidemic. Clonal variation was also seen in the speA and speB genes but at much lower frequency; no variation was detected in the **speC** gene. Erythrogenic **toxin** A was found to be expressed at low levels in all strains; erythrogenic **toxins** B and C were produced in high amounts. All strains were found to harbor the speA, speB, and **speC** genes, regardless of the amount of **toxin** produced. No correlation was found between one specific T1M1 clone and the more serious infections when isolates from bacteremic patients (fatalities or survivors), those with uncomplicated infections, and healthy carriers were compared. Similar results were obtained in a family study in which 3 family members were found to be asymptomatic carriers of the same GAS T1M1 clone as in the bacteremic patient, defined by genotypic and phenotypic experiments.

L10 ANSWER 10 OF 11 TOXLIT
ACCESSION NUMBER: 1980:35585 TOXLIT
DOCUMENT NUMBER: CA-092-191948X
TITLE: Effect of certain antibiotics on the formation of cellular antigens and extracellular products by group-A streptococci.
AUTHOR: Gemmell CG; Abdul Amir MK
CORPORATE SOURCE: Med. Sch., Univ. Glasgow, Glasgow
SOURCE: Pathog. Streptococci, Proc. Int. Symp., 7th, (1979). pp. 67-8.
CODEN: 42XJA6.
FILE SEGMENT: CA
LANGUAGE: English
OTHER SOURCE: CA 92:191948
ENTRY MONTH: 198007
AB Sub-growth-inhibitory concns. of lincomycin (I) and clindamycin (II) strongly decreased cell wall M- and C-antigens of **Streptococcus**, whereas erythromycin (III) and chloramphenicol (IV) had only slight effects. (154-21-2 Lincomycin) (18323-44-9 Clindamycin) (114-07-8 Erythromycin) (56-75-7 Chloramphenicol) The T antigen was not detected in control and III- or IV-treated cultures, but was obsd. in I- or II-treated cultures. None of the major **toxins** or enzymes were formed by the I- or II-treated strains; in the presence of III or IV, hemolysins were formed at control levels but DNase, NADase, and serum-opacity factor prodn. were partially inhibitied. (9003-98-9 DNase) (9032-65-9 NADase) After 30 min incubation, II-treated streptococci were rapidly phagocytized by human **polymorphonuclear**

leukocytes, whereas I-, III-, or V-treated bacteria differed little from the controls. By 60 min, however, both I- and II-treated cells were more greatly ingested than controls or III- or IV-treated cells. The inhibition of M-antigen formation in I- and II-treated streptococci may be related to the enhanced phagocytosis.

L10 ANSWER 11 OF 11 TOXLINE
ACCESSION NUMBER: 1999:181402 TOXLINE
DOCUMENT NUMBER: FEDRIP-1999-07803012
TITLE: Pathogenesis of Streptococcal Skin and Soft Tissue Infections.
AUTHOR: Bisno AlanL M D
CORPORATE SOURCE: Department of Veterans Affairs/Medical Center, Miami, FL
Department of Veterans Affairs/Research and Development.
CONTRACT NUMBER: VA 00213284
SOURCE: FEDRIP DATABASE, NATIONAL TECHNICAL INFORMATION SERVICE (NTIS).
FILE SEGMENT: FEDRIP
LANGUAGE: Unavailable
ENTRY MONTH: 199911
AB RPROJ/FEDRIP **STREPTOCOCCUS** PYOGENES; **STREPTOCOCCAL** INFECTIONS; MOLECULAR BIOLOGY; IMMUNE SYSTEM; CELLULITIS OBJECTIVE: We propose to use a well characterized strain of group A **streptococcus** to explore the relationship of recognized **streptococcal** virulence factors to the expression of skin and soft tissue infection in the murine model. RESEARCH PLAN/METHODOLOGY: Strain 327, isolated from a child with life-threatening pneumonia, produces a lethal necrotizing fasciitis following intracutaneous inoculation of 5X 10x7 colony forming units into the flank of immunocompetent hairless mice. This strain is M-type 1 (the most frequent serotype associated with **streptococcal** necrotizing fasciitis and toxic **streptococcal** syndrome in humans), possesses a hyaluronate capsule, expresses fibronectin binding protein (protein F), and contains the gene encoding **streptococcal** pyrogenic exotoxin B (SpeB) but not SpeA or **SpeC**. In initial experiments we will generate insertion **mutations** in the following genes: emmi (encoding M protein type 1), hasA (hyaluronate capsule), prtF (protein F) and speB in order to assess the effects of these putative virulence factors on the evolution of necrotizing fasciitis. Relative severity of the process will be compared by measurement of lesion size, tissue bacterial concentration, occurrence of extracutaneous dissemination, weight loss, and mortality. In further experiments we shall generate recombinant strains of 327 into which SpeA have been introduced. To assess the influence of SpeA, an attenuated non-lethal infection will be induced by decreasing the inoculum and/or utilizing the less

virulent isogenic variants developed in the previous experiments. Our studies to date, utilizing a virulent M-positive strain of group G **streptococcus** isolated from a human case of cellulitis with bacteremia, have failed to show evidence of protective immunity on multiple repetitive rechallenges, despite the presence of type-specific antibodies to the homologous M-type. This observation, plus the well-known propensity of cellulitis in man to recur, raises questions as to nature and efficacy of the host immune response in **streptococcal** soft tissue infections. We shall attempt to confirm these finding by challenging mice repetitively with a group A **streptococcal** strain (MGAS 158) that produces SpeA and elicits nonlethal cellulitis in the mouse model. Lesions will be allowed to heal completely between challenges. Lesions produced by each challenge will be compared for the features mentioned above. Finally, we shall seek to determine the bacterial etiology of cases of acute cellulitis occurring in patients hospitalized at the Miami Veterans Affairs Medical Center. The causative organisms will be pursued utilizing routine diagnostic techniques (including cultures of blood, throat and toe webs) as well as cultural, immunologic and molecular biologic techniques on biopsies of infected skin. Isolated **streptococcal** organisms will be characterized as to group, type, encapsulation and **toxin** genes. FINDINGS: We have conducted a number of studies with virulent, well-characterized strains of group A **streptococci** in the mouse cellulitis/fasciitis model. In preliminary comparative studies of strains MGAS 327 (SpeA positive, M3) and an isogenic SpeA **mutant**, no difference was found in the lesion size, or mortality between the 2 strains, after either initial or rechallenge. Likewise, no difference was found in lesion size or mortality caused by strain Roselle (M1, SpeA positive) whether or not the mice were immunized with heat-killed organisms before challenge with live organisms. These results are consistent with our previously published results with group G **streptococci**, in which no evidence of protective immunity was found in the murine cellulitis model. All studies summarized above must be confirmed with larger numbers of mice. We are currently testing the ability of immunization with recombinant SpeA (produced in Dr. Collins' laborat

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     FILE 'CAPLUS' ENTERED AT 11:33:45 ON 30 MAR 2000
L11        3430 SEA ABB=ON  PLU=ON  SPEC OR SPE C OR STREPTOCOCC?(5A)C
L12          66 SEA ABB=ON  PLU=ON  L11(S)TOXIN
L13           6 SEA ABB=ON  PLU=ON  L12 AND (MUTAT? OR MUTANT OR
                MUTAGEN? OR POLYMORPH? OR POLY MORPH?)
L14           3 SEA ABB=ON  PLU=ON  L13 NOT L8

L14  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         1999:707302  CAPLUS
DOCUMENT NUMBER:          132:34630
                             Searcher   :    Shears   308-4994
```

TITLE: Epidermal HLA-DR and the enhancement of cutaneous reactivity to superantigenic toxins in psoriasis

AUTHOR(S): Travers, Jeffrey B.; Hamid, Qutayba A.; Norris, David A.; Kuhn, Christine; Giorno, Ralph C.; Schlievert, Patrick M.; Farmer, Evan R.; Leung, Donald Y. M.

CORPORATE SOURCE: Departments of Dermatology and Pharmacology, Indiana University Medical Center, Indianapolis, IN, 46202, USA

SOURCE: J. Clin. Invest. (1999), 104(9), 1181-1189
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Streptococcal and staphylococcal superantigens (SAg's) have been implicated in the pathogenesis of inflammatory skin diseases, but the mechanisms by which these toxins act are unknown. The present study assessed the ability of nanogram quantities of topically applied purified toxic shock syndrome **toxin**-1 (TSST-1), staphylococcal enterotoxin type B, and **streptococcal** pyrogenic enterotoxin types A and **C** to induce inflammatory reactions in clin. uninvolved skin of normal controls and subjects with psoriasis, atopic dermatitis, and lichen planus. These SAg's triggered a significantly greater inflammatory skin response in psoriatics than in normal control subjects or in subjects with atopic dermatitis or lichen planus. Surprisingly, skin biopsies did not exhibit the T-cell receptor V.beta. stimulatory properties predicted for SAg-induced skin reactions. By 6 h after patch testing with SAg's, TNF-.alpha. mRNA had increased in the epidermis (but not the dermis) in biopsies from psoriatics, compared with controls. Immunohistochem. studies revealed significantly higher HLA-DR expression in keratinocytes from psoriatics than from controls. However, a **mutant** TSST-1 protein that fails to bind HLA-DR did not elicit an inflammatory skin reaction. These results indicate that keratinocyte expression of HLA-DR enhances inflammatory skin responses to SAg's. They may also account for previous studies failing to demonstrate selective expansion of T-cell receptor V.beta.s in psoriatics colonized with SAg-producing Staphylococcus aureus, and they identify a novel T cell-independent mechanism by which SAg's contribute to the pathogenesis of inflammatory skin diseases.

L14 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1993:17352 CAPLUS

DOCUMENT NUMBER: 118:17352

TITLE: Genetic diversity in T1M1 group A streptococci in relation to clinical outcome of infection

AUTHOR(S): Norgren, Mari; Norrby, Anna; Holm, Stig E.

Searcher : Shears 308-4994

CORPORATE SOURCE: Dep. CLin. Bacteriol., Univ. Umea, Swed.
SOURCE: J. Infect. Dis. (1992), 166(5), 1014-20
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Genetic diversity was found at high frequency downstream of the emm1 gene among T1M1 group A streptococci (GAS) isolated in Scandinavia during a recent epidemic. Clonal variation was also seen in the speA and speB genes but at much lower frequency; no variation was detected in the speC gene. Erythrogenic toxin A was expressed at low levels in all strains; erythrogenic toxins B and C were produced in high amts. All strains harbored the speA, speB, and **speC** genes, regardless of the amt. of **toxin** produced. No correlation was found between one specific T1M1 clone and the more serious infections when isolates from bacteremic patients (fatalities or survivors), those with uncomplicated infections, and healthy carriers were compared. Similar results were obtained in a family study in which 3 family members were asymptomatic carriers of the same GAS T1M1 clone as in the bacteremic patient, defined by genotypic and phenotypic expts.

L14 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:451311 CAPLUS
DOCUMENT NUMBER: 111:51311
TITLE: Bacteriophage association of streptococcal pyrogenic exotoxin type C
AUTHOR(S): Goshorn, Stephen C.; Schlievert, Patrick M.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: J. Bacteriol. (1989), 171(6), 3068-73
CODEN: JOBAAY; ISSN: 0021-9193
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A gene encoding streptococcal pyrogenic exotoxin type C (SPE C) was isolated from phage DNA derived from Streptococcus pyogenes CS112. The gene, designated speC2, was shown to reside near the phage attachment site of phage CS112. A restriction endonuclease map of the CS112 phage was generated, and the location and orientation of the speC2 gene were detd. Hybridization analyses of eight SPE C-producing strains revealed restriction fragment length **polymorphism** of the speC gene-contg. DNA fragments and further showed that each speC was linked to a common CS112 phage-derived DNA fragment.

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, TOXLIT, TOXLINE' ENTERED AT 11:35:10 ON 30 MAR 2000)
L15 29 S L13
L16 8 S L15 NOT L9
L17 5 DUP REM L16 (3 DUPLICATES REMOVED)

L17 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000015012 MEDLINE
DOCUMENT NUMBER: 20015012
TITLE: Epidermal HLA-DR and the enhancement of cutaneous reactivity to superantigenic toxins in psoriasis [see comments].
COMMENT: Comment in: J Clin Invest 1999 Nov;104(9):1161-4
AUTHOR: Travers J B; Hamid Q A; Norris D A; Kuhn C; Giorno R C; Schlievert P M; Farmer E R; Leung D Y
CORPORATE SOURCE: Department of Dermatology, Indiana University Medical Center, Indianapolis, Indiana 46202, USA.
CONTRACT NUMBER: HL-36577 (NHLBI)
AR-41256 (NIAMS)
HL-37260 (NHLBI)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1999 Nov) 104 (9) 1181-9.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 200002
ENTRY WEEK: 20000204

AB Streptococcal and staphylococcal superantigens (SAg's) have been implicated in the pathogenesis of inflammatory skin diseases, but the mechanisms by which these **toxins** act are unknown. The present study assessed the ability of nanogram quantities of topically applied purified toxic shock syndrome **toxin**-1 (TSST-1), staphylococcal enterotoxin type B, and **streptococcal** pyrogenic enterotoxin types A and C to induce inflammatory reactions in clinically uninvolved skin of normal controls and subjects with psoriasis, atopic dermatitis, and lichen planus. These SAg's triggered a significantly greater inflammatory skin response in psoriatics than in normal control subjects or in subjects with atopic dermatitis or lichen planus. Surprisingly, skin biopsies did not exhibit the T-cell receptor Vbeta stimulatory properties predicted for SAg-induced skin reactions. By 6 hours after patch testing with SAg's, TNF-alpha mRNA had increased in the epidermis (but not the dermis) in biopsies from psoriatics, compared with controls. Immunohistochemical studies revealed significantly higher HLA-DR expression in keratinocytes from psoriatics than from controls. However, a **mutant** TSST-1 protein that fails to bind HLA-DR did not elicit an inflammatory skin reaction. These results indicate that keratinocyte expression of HLA-DR enhances inflammatory skin responses to SAg's.

Searcher : Shears 308-4994

They may also account for previous studies failing to demonstrate selective expansion of T-cell receptor Vbetas in psoriatics colonized with SAg-producing Staphylococcus aureus, and they identify a novel T cell-independent mechanism by which SAg's contribute to the pathogenesis of inflammatory skin diseases.

L17 ANSWER 2 OF 5 TOXLINE
ACCESSION NUMBER: 1996:4266 TOXLINE
DOCUMENT NUMBER: CRISP-96-NS22671-09
TITLE: DYNAMICS OF IRON METABOLISM IN NEUROGLIA.
AUTHOR: CONNOR J R
CORPORATE SOURCE: PENN STATE UNIV/HERSHEY MED CT, PO BOX 850, HERSHEY, PA 17033
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INST OF NEUROLOGICAL DISORDERS AND STROKE.
CONTRACT NUMBER: 5R01NS22671-09
SOURCE: (1995). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199604

AB RPROJ/CRISP Because iron is an essential component of oxidative metabolism and a potent **toxin**, an exquisite system for regulating the availability of iron has been developed. The regulation of iron includes insuring its timely delivery, and sequestering it in a rapidly retrievable form. The brain is highly susceptible to iron induced oxidant damage because of its high iron content (equal to that of liver on a per weight basis), high rate of oxidative metabolism and the high phospholipid content of white matter. Our ultimate goal is to determine (1) the mechanism(s) by which iron homeostasis is maintained in the brain and (2) the specific role(s) for iron in brain metabolism. Our research indicates neuroglial cells are primarily responsible for maintenance of iron homeostasis in brain. Normal expression of the iron mobilization protein, transferrin, its mRNA, and receptor are all dependent upon a normal oligodendrocyte population. Iron itself is found predominantly in oligodendrocytes. This proposal has two components with the common goal of determining the role of glial cells in establishing and maintaining iron homeostasis in the brain. The first component using an in vivo approach will characterize 1) the establishment of normal iron homeostasis during development, 2) the effect of a compromised oligodendrocyte population on establishing iron homeostasis, and 3) the effect of trauma on iron homeostasis. This line of research will test the hypothesis that each glial cell subtype can be recruited to regulate iron access to the brain (neurons). In both trauma and in the absence of

oligodendrocytes astrogliosis occurs. We predict astrocytes become involved in regulating iron access to brain following invasive gliosis, but not in the absence of an invasive injury. In both cases, microglial cells are predicted to increase iron-uptake, ferritin synthesis, etc. The second phase of this proposal uses an in vitro approach to: 1) characterize the parameters associated with iron metabolism such as iron-uptake and transferrin and ferritin synthesis and secretion in neuroglia, 2) identify feedback mechanisms for iron regulation in neuroglia and identify factors which regulate parameters of iron metabolism in glial cells. The hypothesis for this component is that iron metabolism in neuroglial cells is responsive to changes in the milieu. We will focus on iron/transferrin levels, but will eventually examine the effects of hormones, growth factors, cytotoxins, etc. The predicted results are that iron metabolism in each glial cell type will be altered in a manner specific to that cell type. These results would indicate iron has a unique role in the metabolism of each neuroglial cell and that each neuroglial cell has a unique role in attempting to establish iron balance in the neural environment. This line of research is relevant to a number of neurodegenerative disorders including Alzheimer's, Parkinson's, and Multiple Sclerosis and a broad **spec**

L17 ANSWER 3 OF 5 TOXLINE
ACCESSION NUMBER: 1995:208755 TOXLINE
DOCUMENT NUMBER: CRISP-95-NS22671-08
TITLE: DYNAMICS OF IRON METABOLISM IN NEUROGLIA.
AUTHOR: CONNOR J R
CORPORATE SOURCE: PENN STATE UNIV/HERSHEY MED CT, 500 UNIVERSITY DR PO BOX 850, HERSHEY, PA 17033
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INST OF NEUROLOGICAL DISORDERS AND STROKE.
CONTRACT NUMBER: 5R01NS22671-08
SOURCE: (1994). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199507

AB RPROJ/CRISP Because iron is an essential component of oxidative metabolism and a potent **toxin**, an exquisite system for regulating the availability of iron has been developed. The regulation of iron includes insuring its timely delivery, and sequestering it in a rapidly retrievable form. The brain is highly susceptible to iron induced oxidant damage because of its high iron content (equal to that of liver on a per weight basis), high rate of oxidative metabolism and the high phospholipid content of white

matter. Our ultimate goal is to determine (1) the mechanism(s) by which iron homeostasis is maintained in the brain and (2) the specific role(s) for iron in brain metabolism. Our research indicates neuroglial cells are primarily responsible for maintenance of iron homeostasis in brain. Normal expression of the iron mobilization protein, transferrin, its mRNA, and receptor are all dependent upon a normal oligodendrocyte population. Iron itself is found predominantly in oligodendrocytes. This proposal has two components with the common goal of determining the role of glial cells in establishing and maintaining iron homeostasis in the brain. The first component using an in vivo approach will characterize 1) the establishment of normal iron homeostasis during development, 2) the effect of a compromised oligodendrocyte population on establishing iron homeostasis, and 3) the effect of trauma on iron homeostasis. This line of research will test the hypothesis that each glial cell subtype can be recruited to regulate iron access to the brain (neurons). In both trauma and in the absence of oligodendrocytes astrogliosis occurs. We predict astrocytes become involved in regulating iron access to brain following invasive gliosis, but not in the absence of an invasive injury. In both cases, microglial cells are predicted to increase iron-uptake, ferritin synthesis, etc. The second phase of this proposal uses an in vitro approach to: 1) characterize the parameters associated with iron metabolism such as iron-uptake and transferrin and ferritin synthesis and secretion in neuroglia, 2) identify feedback mechanisms for iron regulation in neuroglia and identify factors which regulate parameters of iron metabolism in glial cells. The hypothesis for this component is that iron metabolism in neuroglial cells is responsive to changes in the milieu. We will focus on iron/transferrin levels, but will eventually examine the effects of hormones, growth factors, cytotoxins, etc. The predicted results are that iron metabolism in each glial cell type will be altered in a manner specific to that cell type. These results would indicate iron has a unique role in the metabolism of each neuroglial cell and that each neuroglial cell has a unique role in attempting to establish iron balance in the neural environment. This line of research is relevant to a number of neurodegenerative disorders including Alzheimer's, Parkinson's, and Multiple Sclerosis and a broad **spec**

L17 ANSWER 4 OF 5 TOXLINE
ACCESSION NUMBER: 1994:59551 TOXLINE
DOCUMENT NUMBER: CRISP-94-NS22671-07A1
TITLE: DYNAMICS OF IRON METABOLISM IN NEUROGLIA.
AUTHOR: CONNOR J R
CORPORATE SOURCE: PENN STATE UNIV/HERSHEY MED CT, 500 UNIVERSITY DR PO BOX 850, HERSHEY, PA 17033
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL

INST OF NEUROLOGICAL DISORDERS AND STROKE.
CONTRACT NUMBER: 2R01NS22671-07A1
SOURCE: (1993). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199403

AB RPROJ/CRISP Because iron is an essential component of oxidative metabolism and a potent **toxin**, an exquisite system for regulating the availability of iron has been developed. The regulation of iron includes insuring its timely delivery, and sequestering it in a rapidly retrievable form. The brain is highly susceptible to iron induced oxidant damage because of its high iron content (equal to that of liver on a per weight basis), high rate of oxidative metabolism and the high phospholipid content of white matter. Our ultimate goal is to determine (1) the mechanism(s) by which iron homeostasis is maintained in the brain and (2) the specific role(s) for iron in brain metabolism. Our research indicates neuroglial cells are primarily responsible for maintenance of iron homeostasis in brain. Normal expression of the iron mobilization protein, transferrin, its mRNA, and receptor are all dependent upon a normal oligodendrocyte population. Iron itself is found predominantly in oligodendrocytes. This proposal has two components with the common goal of determining the role of glial cells in establishing and maintaining iron homeostasis in the brain. The first component using an in vivo approach will characterize 1) the establishment of normal iron homeostasis during development, 2) the effect of a compromised oligodendrocyte population on establishing iron homeostasis, and 3) the effect of trauma on iron homeostasis. This line of research will test the hypothesis that each glial cell subtype can be recruited to regulate iron access to the brain (neurons). In both trauma and in the absence of oligodendrocytes astrogliosis occurs. We predict astrocytes become involved in regulating iron access to brain following invasive gliosis, but not in the absence of an invasive injury. In both cases, microglial cells are predicted to increase iron-uptake, ferritin synthesis, etc. The second phase of this proposal uses an in vitro approach to: 1) characterize the parameters associated with iron metabolism such as iron-uptake and transferrin and ferritin synthesis and secretion in neuroglia, 2) identify feedback mechanisms for iron regulation in neuroglia and identify factors which regulate parameters of iron metabolism in glial cells. The hypothesis for this component is that iron metabolism in neuroglial cells is responsive to changes in the milieu. We will focus on iron/transferrin levels, but will eventually examine the effects of hormones, growth factors, cytotoxins, etc. The predicted results are that iron metabolism in each glial cell type will be altered in

a manner specific to that cell type. These results would indicate iron has a unique role in the metabolism of each neuroglial cell and that each neuroglial cell has a unique role in attempting to establish iron balance in the neural environment. This line of research is relevant to a number of neurodegenerative disorders including Alzheimer's, Parkinson's, and Multiple Sclerosis and a broad **spec**

L17 ANSWER 5 OF 5 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1992-323784 [40] WPIDS
CROSS REFERENCE: 1992-270497 [33]; 1992-286398 [35]; 1993-100566 [12]
DOC. NO. CPI: C1992-143866
TITLE: New Bacillus thuringiensis isolate - used for preparing toxin, DNA and transformed hosts for controlling coleoptera insect pests.
DERWENT CLASS: C05 D16
INVENTOR(S): FONCERRADA, L; PAYNE, J M; SICK, A J
PATENT ASSIGNEE(S): (MYCO) MYCOGEN CORP
COUNTRY COUNT: 4
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
CA 2059242	A	19920717	(199240)*		33
NZ 241297	A	19930428	(199320)		
JP 05229913	A	19930907	(199340)		15
US 5366892	A	19941122	(199501)		14

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
CA 2059242	A		CA 1992-2059242	19920113
NZ 241297	A		NZ 1992-241297	19920114
JP 05229913	A		JP 1992-24339	19920116
US 5366892	A	CIP of	US 1991-642112	19910116
			US 1992-812180	19920102

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5366892	A	CIP of	US 5277905

PRIORITY APPLN. INFO: US 1992-812180 19920102; US 1991-642112 19910116
AN 1992-323784 [40] WPIDS
CR 1992-270497 [33]; 1992-286398 [35]; 1993-100566 [12]
Searcher : Shears 308-4994

AB CA 2059242 A UPAB: 19990511
The following are claimed: (A) a process for controlling coleopteran insect pests which comprises contacting the insect pests with Bacillus thuringiensis (B.t.) NRLL B-18746 or **mutants**; (B) a process for controlling soil-inhabiting insect pests of the order Coleoptera which comprises (a) preparing a bait granule comprising B.t. PS50C or its **mutants**, spores or crystals; and (b) placing the bait granule on or in the soil; (C) a compsn. comprising B.t. PS50C or its **mutants**, spores or crystals in association with a carrier; (D) a compsn. comprising B.t. PS50C or its **mutants** in association with formulation ingredients applied as a seed coating; (E) a biologically pure culture of B.t. PS50C, NRRL B-18746, or its **mutants**, having activity against insect pests of the order Coleoptera; (F) a **toxin** active against coleopteran pests, which **toxin** is producible by B.t. PS50C NRRL B-18746, where the **toxin** has a molecular wt. of 130 kD and a predicted peptide sequence as defined in the **spec**.

Specifically claimed are the plasmid pMYC 1638 and E.coli NM 522 (pMYC 1638).

USE - The polypeptide toxin can be used for controlling coleopteran insect pests, partic. Colorado potato beetle

Dwg.0/2

ABEQ US 5366892 A UPAB: 19950110
Isolated polynucleotide encoding a Bacillus thuringiensis toxin active against coleopteran pests has a mol.wt. of about 130 kD and a predicted peptide sequence given in the specification.

USE - Used for controlling coleopteran insects on crops.

Dwg.0/2

FILE 'CAPLUS' ENTERED AT 11:36:55 ON 30 MAR 2000
L18 4 S L12 AND VACCIN?
L19 3 S L18 NOT (L8 OR L13)

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:15329 CAPLUS
DOCUMENT NUMBER: 132:61291
TITLE: Methods of expanding and selecting disease associated T-cells using antigen-presenting cells and disease associated antigens
INVENTOR(S): Kaltoft, Keld; Agnholt, Jorgen
PATENT ASSIGNEE(S): Den.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000587	A1	20000106	WO 1999-DK363	19990625

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	
DK 1998-848	19980626
DK 1998-895	19980701
US 1998-91684	19980702

AB Methods of expanding and selecting disease assocd. T-cells, continuous T-cell lines as well as T-cell lines obtainable by these methods are disclosed. Furthermore, pharmaceutical compns. and **vaccines** comprising activated disease assocd. T-cell are disclosed. The uses of the T-cell and T-cell lines are numerous and include methods of diagnosis, methods for the treatment, alleviation or prevention of diseases assocd. with activation of T-cells, methods of testing the effect of medicaments against T-cell assocd. diseases, methods of detecting T-cell growth factors, methods of monitoring the response to treatment, alleviation or prevention of diseases assocd. with activation of T-cells, and methods of identifying disease assocd. antigens. Peripheral blood mononuclear cells were cultured with IL-2 and IL-4 and allostimulated with Psor-2 cells, a T-cell line from a patient with psoriasis vulgaris.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1998:682420 CAPLUS
DOCUMENT NUMBER:	129:314963
TITLE:	Peptides useful for reducing symptoms of toxic shock syndrome
INVENTOR(S):	Bannan, Jason D.; Zabriskie, John B.
PATENT ASSIGNEE(S):	The Rockefeller University, USA
SOURCE:	PCT Int. Appl., 70 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9845325	A1	19981015	WO 1998-US6663	19980401

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP,

KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9869501	A1	19981030	AU 1998-69501	19980401
EP 973803	A1	20000126	EP 1998-915277	19980401

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	US 1997-838413	19970407
	WO 1998-US6663	19980401

AB This invention relates to compns. and methods for eliciting an immunogenic response in mammals, including responses which provide protection against, or reduce the severity, of toxic shock from bacterial infections. Peptides derived from homologous sequences of the family of staphylococcal and streptococcal toxins are used to induce serum antibodies. These peptide-induced antibodies exhibited neutralizing activity for the toxins. In addn., the invention also relates to diagnostic assays and kits to detect the presence of antibodies to staphylococcal and streptococcal toxins. Isolated and purified nucleic acids encoding these immunogenic peptides are claimed.

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1995:220719 CAPLUS
DOCUMENT NUMBER:	122:7963
TITLE:	Method for treating Kawasaki syndrome via immune modulation
INVENTOR(S):	Kotzin, Brian; Marrack, Philippa; Kappler, John; Leung, Donald
PATENT ASSIGNEE(S):	National Jewish Center for Immunology and Respiratory Medicine, USA
SOURCE:	PCT Int. Appl., 50 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9422474	A1	19941013	WO 1994-US3719	19940405

W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9465554	A1	19941024	AU 1994-65554	19940405
JP 08508734	T2	19960917	JP 1994-522468	19940405
PRIORITY APPLN. INFO.:			US 1993-42876	19930405
			WO 1994-US3719	19940405

AB The invention relates to various methodologies for diagnosing and treating Kawasaki syndrome. Various bacteria, including TSST-1 producing Staphylococcus aureus, and streptococcal erythrogenic **toxin** B and **streptococcal** erythrogenic **toxin** C producing **streptococcus** have been found to be indicative of the pathol. condition. The superantigen or superantigen deriv. are used as **vaccine** for preventing or treating Kawasaki syndrome.

(FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, TOXLIT, TOXLINE' ENTERED AT 11:41:07 ON 30 MAR 2000)

L20 9 S L18
L21 6 S L20 NOT (L9 OR L16)
L22 3 DUP REM L21 (3 DUPLICATES REMOVED)

L22 ANSWER 1 OF 3 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92362647 EMBASE
DOCUMENT NUMBER: 1992362647
TITLE: Screening for Corynebacterium diphtheriae.
AUTHOR: Wilson A.P.R.; Matthews S.; Bahl M.; Efstratiou A.; Cookson B.D.
CORPORATE SOURCE: Department of Clinical Microbiology, University College/Middlesex Hosp.,London WC1E 6AU, United Kingdom
SOURCE: Journal of Clinical Pathology, (1992) 45/11 (1036-1037).
ISSN: 0021-9746 CODEN: JCPAAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
007 Pediatrics and Pediatric Surgery
011 Otorhinolaryngology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A throat swab from a 9 year old girl with pharyngitis yielded a non-toxigenic strain of Corynebacterium diphtheriae var mitis and **Streptococcus** group G. C pseudodiphtheriticum was isolated from the throats of two of her four brothers. In each case the isolate was sent to the reference laboratory before full identification. The growth was found to be mixed for one brother; the other isolate being a **toxin** producing C diphtheriae var gravis. The child was asymptomatic and the case proves that all colonial types on the Hoyles plate should be identified.

L22 ANSWER 2 OF 3 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1991-166115 [23] WPIDS
DOC. NO. CPI: C1991-071889
TITLE: DNA sequence encoding tetanus toxin fragment C - useful in the manufacture of **vaccines** for immunity to tetanus utilising yeast as host organism.
DERWENT CLASS: B04 D16
INVENTOR(S): CLARE, J J; FAIRWEATHE, N F; MAKOFF, A J; ROMANOS, M A; FAIRWEATHER, N F
PATENT ASSIGNEE(S): (WELL) WELLCOME FOUND LTD; (WELL) WELLCOME FOUNDATION LTD; (EVAN) EVANS MEDICAL LTD
COUNTRY COUNT: 15
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 430645	A	19910605	(199123)*		50
R: AT BE CH DE ES FR GB IT LI LU NL SE					
JP 03285681	A	19911216	(199205)		
EP 430645	A3	19920102	(199320)		50
EP 430645	B1	19930818	(199333)	EN	52
R: AT BE CH DE DK ES FR GB IT LI LU NL SE					
DE 69002817	E	19930923	(199339)		
ES 2058821	T3	19941101	(199444)		
US 5389540	A	19950214	(199512)		44
US 5571694	A	19961105	(199650)		40
JP 3003211	B2	20000124	(200009)		41

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 430645	A		EP 1990-312870	19901127
JP 03285681	A		JP 1990-328729	19901128
EP 430645	A3		EP 1990-312870	19901127
EP 430645	B1		EP 1990-312870	19901127
DE 69002817	E		DE 1990-602817	19901127
			EP 1990-312870	19901127
ES 2058821	T3		EP 1990-312870	19901127
US 5389540	A		US 1990-618312	19901127
US 5571694	A	Cont of	US 1990-618312	19901127
			US 1994-280228	19940725
JP 3003211	B2		JP 1990-328729	19901128

FILING DETAILS:

PATENT NO	KIND	PATENT NO

Searcher : Shears 308-4994

DE 69002817	E	Based on	EP 430645
ES 2058821	T3	Based on	EP 430645
US 5571694	A	Cont of	US 5389540
JP 3003211	B2	Previous Publ.	JP 03285681

PRIORITY APPLN. INFO: GB 1989-26832 19891128; GB 1990-6097 19900317

AN 1991-166115 [23] WPIDS

AB EP 430645 A UPAB: 19931113

The sequence (I) has an increased (G+C)-content relative to the wild-type DNA sequence so as to allow the production of complete MRNA transcripts in yeast. The increased (G+C)-content is especially 47% (c.f. 29% in wild type). Also new are an expression vector containing (I) and a yeast organism transformed with the vector.

USE/ADVANTAGE - (I) is used in the manufacture of a **vaccine** for conferring immunity to tetanus (claimed). The use of yeast as a host organism overcomes the need to exclude toxic pyrogenic factors seen in the product when E. coli is the host. **Vaccine** contains a final concentration of e.g. 0.2-200 (especially 30) microg/ml of fragment C and 0.1-2 (especially 0.5)ml is administered.

In an example, Balb/C mice were **vaccinated** (0.5 ml), challenged 4 weeks later with 100LD50 of tetanus toxin and survivors counted 4 days later. Yeast intracellular fragment C had at least equal potency to E. coli produced material. @(50pp Dwg.No.0/17)

0/17

ABEQ EP 430645 B UPAB: 19931119

A DNA sequence encoding tetanus toxin fragment C and having a (G+C)-content that has been increased in the region from nucleotide 410 to the 3' end of the coding sequence relative to the wild-type DNA sequence so as to allow the production of complete mRNA transcripts in yeast, the nucleotide numbering corresponding to that set forth in SEQ ID NOS:1 and 2.

Dwg.0/17

ABEQ US 5389540 A UPAB: 19950328

Expression vector contains recombinant DNA that encodes the prodn. of an active tetanus **toxin** fragment C having a defined aminoacid sequence; and the nucleotide sequence of the recombinant DNA is also defined, exhibiting an enhanced G and C content compared with the natural DNA, **spec**. in nucleotide fragments 510-710; 650-850; 800-1,100; 900-1,200; and 1,100-1,356. Host yeast cells have been transformed with these vectors and then propagated to produce the heterologous **toxin** fragment C.

USE - The recombinant toxin is the active component of improved **vaccines** against tetanus.

ADVANTAGE - The active fragment is non-toxic yet a powerful immunising agent.

Dwg.0/0

ABEQ US 5571694 A UPAB: 19961211

An expression vector which incorporates a 1359 base DNA sequence encoding tetanus toxin fragment C, which has a 452 amino acid sequence, and has an increased (G+C)-content relative to the wild-type DNA sequence in each of the following regions:

(i) from nucleotide 510 to nucleotide 710,
(ii) from nucleotide 650 to nucleotide 850,
(iii) from nucleotide 800 to nucleotide 1100,
(vi) from nucleotide 900 to nucleotide 1200 and,
(v) from nucleotide 1100 to nucleotide 1356,

that expresses said fragment C in yeast, all sequences are given in the specification.

Dwg.0/17

L22 ANSWER 3 OF 3 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 90060824 MEDLINE
DOCUMENT NUMBER: 90060824
TITLE: Plasmid vectors for constructing translational fusions to the B subunit of cholera toxin.
AUTHOR: Dertzbaugh M T; Macrina F L
CORPORATE SOURCE: Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond 23298-0678.
CONTRACT NUMBER: R37 DE04224 (NIDCR)
SOURCE: GENE, (1989 Oct 30) 82 (2) 335-42.
Journal code: FOP. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003

AB A family of plasmid cloning vectors has been developed for creating translational fusions to the ctxB gene encoding the B subunit of cholera **toxin** (CTB) in Escherichia coli. These vectors permit insertion of transcriptionally and translationally competent gene sequences upstream from ctxB. To test the utility of the system, a portion of the glucosyltransferase B (GTF) gene (gtfB) from the cariogenic bacterium **Streptococcus** mutans GS-5 (Bratthall serotype **c**), encoding the N-terminal one-third of the protein, was inserted into each vector. E. coli lysates containing the constructs were partially purified by passage over a GM1 ganglioside affinity column. Western blotting analysis of the column retentate from one of the lysates revealed the presence of a novel 58-kDa protein which cross-reacted with antisera to GTF and CTB. These vectors are of general use for making other translational fusions to ctxB. The high binding affinity of CTB can be exploited in purifying large polypeptides fused to this relatively small protein. Moreover, these vectors can be used to create neoantigens with altered immunogenicity for use in polypeptide-based **vaccines**.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, LIFESCI, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, TOXLIT, TOXLINE' ENTERED AT 11:43:03 ON 30 MAR 2000)

- Author (s)

L23	1515	SEA ABB=ON	PLU=ON	SCHLIEVERT P?/AU
L24	611	SEA ABB=ON	PLU=ON	OHLENDORF D?/AU
L25	10559	SEA ABB=ON	PLU=ON	MITCHELL D?/AU
L26	34	SEA ABB=ON	PLU=ON	GAHR P?/AU
L27	2	SEA ABB=ON	PLU=ON	L23 AND L24 AND L25 AND L26
L28	160	SEA ABB=ON	PLU=ON	L23 AND (L24 OR L25 OR L26)
L29	47	SEA ABB=ON	PLU=ON	L24 AND (L25 OR L26)
L30	2	SEA ABB=ON	PLU=ON	L25 AND L26
L31	12510	SEA ABB=ON	PLU=ON	L23 OR L24 OR L25 OR L26
L32	135	SEA ABB=ON	PLU=ON	(L28 OR L29 OR L31) AND L12
L33	10	SEA ABB=ON	PLU=ON	L32 AND (MUTAT? OR MUTANT OR MUTAGEN? OR POLYMORPH? OR POLY MORPH?)
L34	10	SEA ABB=ON	PLU=ON	L27 OR L30 OR L33
L35	5	DUP REM L34 (5 DUPLICATES REMOVED)		

L35 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1

ACCESSION NUMBER: 1999:707302 CAPLUS
DOCUMENT NUMBER: 132:34630
TITLE: Epidermal HLA-DR and the enhancement of cutaneous reactivity to superantigenic toxins in psoriasis
AUTHOR(S): Travers, Jeffrey B.; Hamid, Qutayba A.; Norris, David A.; Kuhn, Christine; Giorno, Ralph C.; **Schlievert, Patrick M.**; Farmer, Evan R.; Leung, Donald Y. M.
CORPORATE SOURCE: Departments of Dermatology and Pharmacology, Indiana University Medical Center, Indianapolis, IN, 46202, USA
SOURCE: J. Clin. Invest. (1999), 104(9), 1181-1189
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Streptococcal and staphylococcal superantigens (SAg's) have been implicated in the pathogenesis of inflammatory skin diseases, but the mechanisms by which these toxins act are unknown. The present study assessed the ability of nanogram quantities of topically applied purified toxic shock syndrome **toxin**-1 (TSST-1), staphylococcal enterotoxin type B, and **streptococcal** pyrogenic enterotoxin types A and **C** to induce inflammatory reactions in clin. uninvolved skin of normal controls and subjects with psoriasis, atopic dermatitis, and lichen planus. These SAg's triggered a significantly greater inflammatory skin response in psoriatics than in normal control subjects or in subjects with atopic dermatitis or lichen planus. Surprisingly, skin biopsies did not exhibit the T-cell receptor V.beta. stimulatory properties

predicted for SAg-induced skin reactions. By 6 h after patch testing with SAg's, TNF-.alpha. mRNA had increased in the epidermis (but not the dermis) in biopsies from psoriatics, compared with controls. Immunohistochem. studies revealed significantly higher HLA-DR expression in keratinocytes from psoriatics than from controls. However, a **mutant** TSST-1 protein that fails to bind HLA-DR did not elicit an inflammatory skin reaction. These results indicate that keratinocyte expression of HLA-DR enhances inflammatory skin responses to SAg's. They may also account for previous studies failing to demonstrate selective expansion of T-cell receptor V.beta.s in psoriatics colonized with SAg-producing Staphylococcus aureus, and they identify a novel T cell-independent mechanism by which SAg's contribute to the pathogenesis of inflammatory skin diseases.

L35 ANSWER 2 OF 5 TOXLINE
ACCESSION NUMBER: 1999:51994 TOXLINE
DOCUMENT NUMBER: CRISP-99-HL36611-11
TITLE: CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR: **SCHLIEVERT P M**
CORPORATE SOURCE: UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER: 5R01HL36611-11
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904
AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic **toxin** superantigens, notably streptococcal pyrogenic exotoxins (SPEs, scarlet fever **toxins**), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome **toxin**-1, with the intent to clarify the molecular mechanism(s) of action of the **toxins** and develop toxoid vaccines against the **toxins**. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient **toxins** for structural analyses by ethanol

precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic **toxin** superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

L35 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
ACCESSION NUMBER: 1998:398420 CAPLUS
DOCUMENT NUMBER: 129:53355
TITLE: **Mutants** of **streptococcal toxin C** and use as vaccines
INVENTOR(S): **Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.**
PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA; Schlievert, Patrick M.; Ohlendorf, Douglas; Mitchell, David T.; Gahr, Pamala J.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9824910	A2	19980611	WO 1997-US22125	19971205

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,

FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9876256	A1	19980629	AU 1998-76256	19971205
EP 946730	A2	19991006	EP 1997-949733	19971205

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	US 1996-33251	19961206
	WO 1997-US22125	19971205

AB This invention is directed to **mutants** of Streptococcus pyrogenes exotoxin type C (SPE-C) or fragments thereof, vaccine and pharmaceutical compns., and methods of using the vaccine and pharmaceutical compns. The preferred **SPE-C toxin** has at least one amino acid change and is substantially non-lethal compared with the wild type **SPE-C toxin**. The **mutant SPE-C toxins** can form vaccine compns. useful to protect animals against the biol. activities of wild type **SPE-C toxin**. Single and double substitution **mutants** of SPE-C were prepd. with E. coli. Rabbits immunized with these recombinant toxins were protected from challenge by S. pyogenes.

L35 ANSWER 4 OF 5 TOXLINE

ACCESSION NUMBER:	1998:60283 TOXLINE
DOCUMENT NUMBER:	CRISP-98-HL36611-10
TITLE:	CARDIOTOXICITY OF STREPTOCOCCAL PYROGENIC EXOTOXIN.
AUTHOR:	**SCHLIEVERT P M**
CORPORATE SOURCE:	UNIVERSITY OF MINNESOTA, 420 DELAWARE ST SE BOX 196 UMH, MINNEAPOLIS, MN 55455-0312 U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE.
CONTRACT NUMBER:	2R01HL36611-10
SOURCE:	(1997). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY:	United States
DOCUMENT TYPE:	(RESEARCH)
FILE SEGMENT:	CRISP
LANGUAGE:	English
ENTRY MONTH:	199805

AB RPROJ/CRISP DESCRIPTION (Adapted from the applicant's abstract): The long term goals of this project are two fold: a) to evaluate the role of pyrogenic **toxin** superantigens, notably streptococcal pyrogenic exotoxins (SPEs, scarlet fever **toxins**), in causing both acute toxic shock syndrome and vascular illnesses and chronic autoimmune and allergic diseases, and b) to analyze the structure-function relationships among the SPEs and between the SPEs and staphylococcal enterotoxins and toxic shock syndrome **toxin**-1, with the intent to clarify the molecular

mechanism(s) of action of the **toxins** and develop toxoid vaccines against the **toxins**. Specific aims of the present application include: a) determination of the three dimensional structure of **SPE C** and SPEA/staphylococcal enterotoxin C (SEC/SEB complexed. with the T cell receptor beta chain. The investigator's role in these studies is to provide sufficient **toxins** for structural analyses by ethanol precipitation from culture fluids, resolubilization in acetate buffered saline at pH 4.0 or water, and preparative isoelectric focusing. Crystallization and three dimensional structure analysis of **SPE C** will be done in collaboration with Dr. Douglas H. Ohlendorf, Department of Biochemistry, University of Minnesota and that of SPE A/SEB complexed to the beta chain of the T cell receptor by Dr. Roy A.. Mariuzza, Center for Advanced Research in Biotechnology, University of Maryland; b) Domains and amino acid residues on **SPE C** and the SPE A/SEC/SEB subgroup of pyrogenic **toxin** superantigens required for biological activity (pyrogenicity, enhancement of lethal endotoxin shock and cardiotoxicity, ability to induce TSS when administered subcutaneously in miniosmotic pumps, superantigenicity, and lipopolysaccharide binding) will be localized through use of PCR **mutagenesis**. Nucleotide sequencing will be done to verify changed amino acids and structural analysis where possible to assess alterations of three dimensional structure of **mutants**. It is hoped in addition to localizing domains required for toxicity, that these studies will clarify important mechanisms of T cell activation and lead to useful toxoid vaccines.

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ACCESSION NUMBER:	1989:451311 CAPLUS
DOCUMENT NUMBER:	111:51311
TITLE:	Bacteriophage association of streptococcal pyrogenic exotoxin type C
AUTHOR(S):	Goshorn, Stephen C.; **Schlievert, Patrick M.**
CORPORATE SOURCE:	Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
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AB A gene encoding streptococcal pyrogenic exotoxin type C (SPE C) was isolated from phage DNA derived from Streptococcus pyogenes CS112. The gene, designated speC2, was shown to reside near the phage attachment site of phage CS112. A restriction endonuclease map of the CS112 phage was generated, and the location and orientation of the speC2 gene were detd. Hybridization analyses of eight SPE C-producing strains revealed restriction fragment length **polymorphism** of the speC gene-contg. DNA fragments and